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Wesley Tang
Department of Medicine, Kettering Medical Center, Kettering, OH, USA, wesley.tang@ketteringhealth.org

Lex Leonhardt
Department of Medicine, Kettering Medical Center, Kettering, OH, USA

Aamir Pervez
Department of Medicine, Kettering Medical Center, Kettering, OH, USA

Satish Sarvepalli
Division of Infectious Disease, South Dayton Acute Care Consultants, Dayton, OH, USA

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CASE REPORT

A Case of Pleural Tuberculosis vs Latent Tuberculosis Reactivation as a Result of COVID-19 Infection and Treatment

Wesley Tang [a,*], Lex Leonhardt [a], Aamir Pervez [a], Satish Sarvepalli [b]

[a] Department of Medicine, Kettering Medical Center, Kettering, OH, USA
[b] Division of Infectious Disease, South Dayton Acute Care Consultants, Dayton, OH, USA

Abstract

The reactivation of latent tuberculosis occurs when a patient living with *Mycobacterium tuberculosis* enters a state where the immune system is suppressed. Since early 2021, the standard of care has been to provide corticosteroids in patients with COVID-19 infection in hospitalized patients receiving supplemental oxygen or mechanical ventilation. The immunomodulatory effects of corticosteroids are potentially detrimental for patients with latent vs active tuberculosis, with concomitant SARS-CoV2 infection. We present one of the first few cases in the literature detailing a case of reactivation of latent tuberculosis vs. pleural tuberculosis as a consequence of COVID-19, and who underwent subsequent corticosteroid treatment.

Keywords: Pleural tuberculosis, Latent tuberculosis, Tuberculosis reactivation, COVID-19 infection, Immunosuppression, Corticosteroids

1. Introduction

Pulmonary tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis*, with 1.2−1.4 million deaths attributed to TB in 2019 globally.[1] In immunocompetent patients, tuberculosis is often in a latent state as defined by a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically active TB.[2] Latent tuberculosis remains dormant until reactivated when the immune system is suppressed. It is estimated that 20%−30% of the world's population is latently infected with tuberculosis.[3] The risk for reactivation depends largely on the state of a person's immunological status.[4] Meanwhile, the global COVID-19 pandemic has resulted in over 185 million cases with more than 4 million deaths.[5] Since the RECOVERY trial, the standard of care has been to provide dexamethasone in hospitalized patients receiving supplemental oxygen or mechanical ventilation.[6] Corticosteroids, such as dexamethasone, cause immunomodulatory effects and are now considered the standard of care for a subset of COVID-19 infections. These immunomodulatory effects may be detrimental to patients living with latent TB and concomitant COVID-19 infection. We present a case of a patient born in Rwanda, developed latent TB, who later immigrated to the United States in 2014, and contracted COVID-19 requiring hospitalization. As part of his clinical course, corticosteroids were provided for his COVID-19 pneumonia, and the patient subsequently developed reactivation of latent tuberculosis vs worsening of pleural TB.

2. Case description

A 33-year-old native of the Democratic Republic of the Congo with history of occupational TB exposure in Rwanda six years prior to presentation initially presented to the emergency department complaining of a five day history of exertional dyspnea, mid-epigastric pain, high fevers, (Tmax 101.9 F) and fatigue. The patient reported that he was a healthcare

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* Corresponding author at: Kettering Medical Center, Department of Medical Education, 3535 Southern Blvd Dayton, OH, 45429, USA.
E-mail address: Wesley.tang@ketteringhealth.org (W. Tang).

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worker in a TB clinic and delivered anti-tuberculous medications to patients with active pulmonary TB. He reported a positive Quantiferon Gold TB screening in 2014 with negative chest x-ray. He also denied ever receiving treatment for latent tuberculosis. At no point did the patient ever complain of cough, night sweats, or weight loss.

He was admitted to the COVID-19 unit due to elevated clinical suspicion for COVID-19 pneumonia. Computed tomography (CT) chest without contrast demonstrated evidence of diffuse ground-glass opacities, peri-pancreatic inflammation, and a moderate right-sided pleural effusion (Fig. 1). A pancreatic pseudocyst of 33 mm × 30 mm x 23 mm was noted and subsequently confirmed on MRI-liver with and without contrast. Lipase was non-elevated at 216 U/L. He underwent right sided thoracentesis with 350 cc fluid drained, with total serum protein 6.8 g/dL, pleural fluid protein 5.7 g/dL, serum LDH 129 U/L, pleural fluid LDH 315 U/L, indicating an exudative process by Light's criteria. Cytology, acid fast bacilli (AFB) smear and culture were sent for evaluation and were subsequently negative after 6 weeks. Serum antigen HIV testing was non-reactive. With resolution of symptoms, the patient was subsequently discharged with diagnoses of right sided pleural effusion induced by pancreatitis with incidental finding of a pancreatic cyst and was instructed to follow up outpatient with pulmonology and gastroenterology.

The patient was evaluated by outpatient pulmonology two months later and was found to have recurrent right pleural effusion, requiring repeat thoracentesis that again demonstrated cytology negative exudative process (serum protein 6.8 g/dL, pleural fluid protein 5.4 g/dL, serum LDH 140 U/L, pleural fluid LDH 252 U/L). Pleural adenosine deaminase (ADA) was sent and resulted at 7.6 U/L (reference range 0–9.4 U/L). One month after outpatient thoracentesis, he was again admitted to the hospital due to worsening dyspnea and was found to have a recurrent large right pleural effusion requiring repeat thoracentesis. SARS-CoV-2 Polymerase Chain Reaction (PCR) testing returned positive and the patient was admitted to the COVID-19 medical floor. Oral dexamethasone 6 mg daily was initiated. 1650 cc green-yellow pleural fluid was aspirated and sent for fluid analysis with similar findings of an exudative process by Light's criteria as above. Additional analyses performed included flow cytometry that did not demonstrate immunophenotypic evidence of a monotypic B-cell or aberrant T-cell population. Pleural fluid studies including fluid differential, ADA, cholesterol, amylase, triglycerides, and glucose, did not display abnormalities. Post-thoracentesis chest x-ray demonstrated a significant amount of residual pleural fluid, warranting consultation with cardiothoracic (CT) surgery for consideration of video-assisted thoracoscopic surgery (VATS) with biopsy and pleurodesis to be scheduled as an outpatient. The patient remained hemodynamically stable without the need for supplemental oxygen and was discharged home after 2 days. He completed a 7-day course of dexamethasone. Pre-operative 2D echocardiogram demonstrated a left ventricular ejection fraction of 56% without diastolic or valvular abnormalities.

Unfortunately, the patient's VATS with pleurodesis was canceled as the patient did not follow up with CT surgery.

One month later the patient returned to the emergency department complaining of recurrent left-sided pleuritic chest pain and high fevers at home. On arrival he had a fever of 102.4 F with

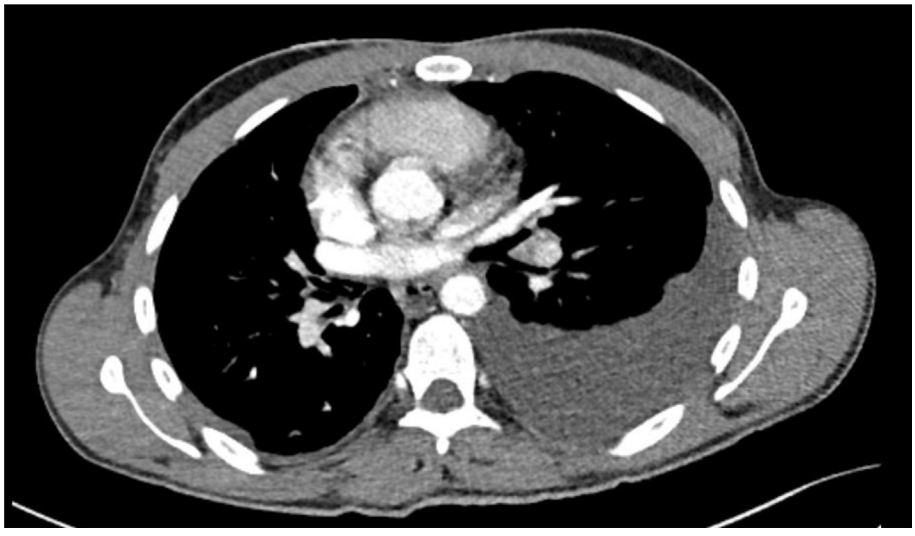

Fig. 1. CT angiogram with PE protocol demonstrating large left pleural effusion at time of COVID-19 pneumonia diagnosis.

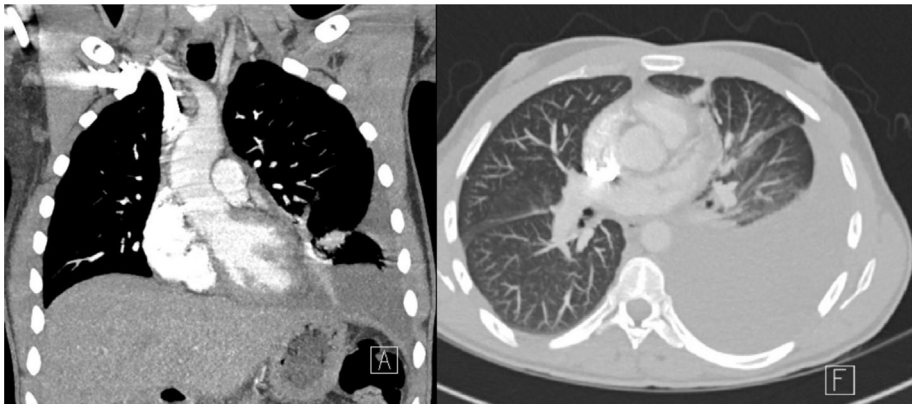

Fig. 2. Computed tomography of the chest demonstrating large left pleural effusion with compressive atelectasis one month after COVID-19 diagnosis.

otherwise stable hemodynamics and no oxygen requirement. CT angiogram with PE protocol was again performed demonstrating a large left pleural effusion (Fig. 2). Previous imaging of the pancreatic pseudocyst measuring 33 × 30 × 23 mm showed a decrease in size compared to previous exam and was now measured as 25 × 19 × 17 mm. Pulmonology and cardiothoracic surgery were consulted and left VATS with pleurectomy, pleurodesis, pleural and diaphragm biopsy and cultures with evacuation of left pleural effusion was performed on hospital day two. Intraoperatively, green-tinted serous pleural fluid with diffuse studding of vesicles papules and plaques on the parietal pleura, visceral pleura, and diaphragm were noted (Fig. 3). In regards to previously visualized pancreatic cyst, gastroenterology and surgical oncology were consulted, however opted to manage conservatively with outpatient surveillance MRI due to decreasing size of the collection. Pathology of pleural, diaphragmatic and pleural peel tissue demonstrated organizing fibrous tissue with fibrinous exudate as well as areas of granulomatous inflammation. There was evidence of central areas of necrosis in multiple granulomas. Special stains for acid-fast and fungal organisms were negative. Pleural fluid ADA was performed with ARUP Laboratories and was interpreted as within normal limits at 18 U/L (reference range 0–30 U/L). Multiple AFB cultures and smears from pleural fluid, chest wall tissue, and pleural tissue were collected and sent for analysis.

Given granulomatous changes on pathology, the patient was transferred to a negative pressure room with airborne precautions and serum QuantiFERON Gold testing was ordered due to elevated suspicion for pleural tuberculosis. QuantiFERON Tb Gold Plus resulted positive. Infectious disease was

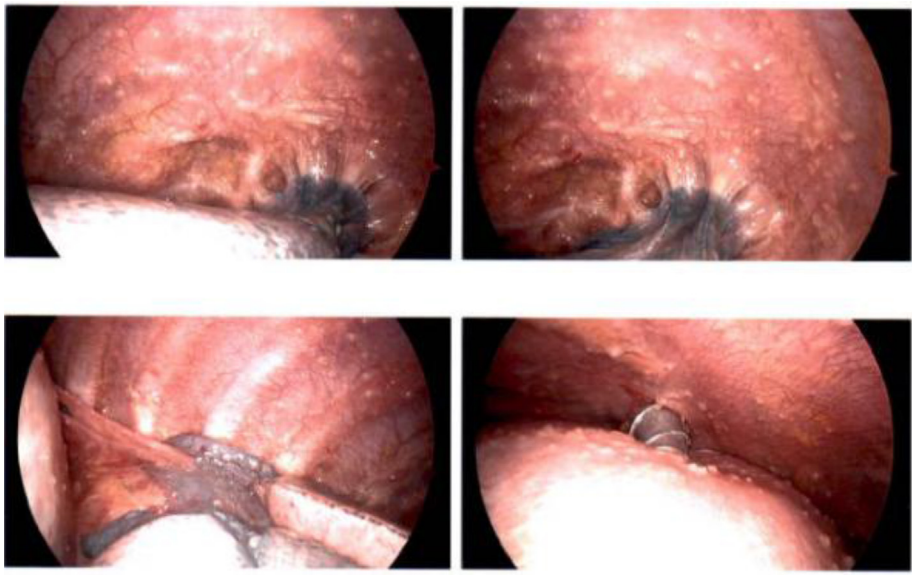

Fig. 3. Diffuse studding of vesicles, papules and plaques on the parietal pleura, visceral pleura, and diaphragm intraoperatively at the time of left video-assisted thoracoscopy.

consulted and recommended initiation of treatment for pleural TB with a four-drug regimen including rifampin 600 mg daily, isoniazid 300 mg daily, pyrazinamide 1500 mg daily, ethambutol 1200 mg daily and supplemental pyridoxine 50 mg daily. The State Department of Health was notified of findings and assumed care of the patient with initiation of contact tracing and further testing as appropriate. AFB cultures and smears from pleural fluid, chest wall tissue and pleural tissue resulted negative for acid fast bacilli after six weeks.

Following initiation of TB medications and VATS surgery, the patient has not had a recurrence of dyspnea or pleural effusions. He remains symptom free 1 year from initiation and completion of antimicrobial therapy.

3. Discussion

Patients with severe COVID-19 infections have high systemic levels of inflammatory molecules, aka "cytokine storm", with notable elevations in interleukins (IL-2, IL-6, IL-10), inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor-alpha (TNF-α). It is unknown what these immunomodulatory effects may have on the reactivation of latent TB into active TB. In contrast, corticosteroids have a multitude of anti-inflammatory properties, with modulation of mitochondrial functions, metabolism, and the stress response via differential regulation of various effector molecules.[7] At present, corticosteroids (dexamethasone) alone, or in conjunction with remdesivir remains the standard of care in hospitalized patients requiring high-flow oxygen or noninvasive ventilation with COVID-19.[8] The use of corticosteroids in the treatment of COVID-19, could predispose individuals with latent TB to reactivate into active tuberculosis infection.

To date, a PubMed search using terms: "latent", "tuberculosis", "reactivation", "COVID-19", have uncovered four cases associating active TB with SARS-CoV2 infection.[9–11] These reports do not detail patients with latent TB with subsequent reactivation of TB. To the author's knowledge, the present case may be the first case report in the literature detailing reactivation of TB, or a case of pleural TB, in a patient treated for COVID-19. Furthermore, there are no guidelines at present to screen patients for TB prior to initiating corticosteroid therapy in patients with COVID-19. Given the lack of epidemiological data or case reports, non-pulmonary TB or reactivation of latent tuberculosis may be underrecognized and underreported in patients with COVID-19 undergoing corticosteroid treatment.

With the present case, it is difficult to determine whether our patient's case represented pleural TB with concomitant COVID-19 infection, or reactivation of latent TB with concomitant COVID-19 infection. Furthermore, if there was reactivation of latent TB, it is also indeterminate whether reactivation was caused by the immunomodulatory effects from COVID-19 infection, or whether the reactivation of TB was caused by systemic glucocorticoid therapy. The authors speculate that pleural TB worsened by COVID-19 infection and treatment is more likely to cause the above presentation given that the patient presented with pleural effusions prior to COVID-19 diagnosis.

Author contributions statement

WT, LL, AP designed and conducted the research. SS provided the data. WT had primary responsibility for the final content. All authors read and approved the final manuscript.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Statement of ethics

Kettering Health Network Institutional Review Board oversees all scholarly activities across its facilities and determined that case reports meet the criteria for exempt review, and do not meet the definition of human research.

Consent to participate

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Conflicts of interest

The authors declare that they do not have a conflict of interest.

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